Fertility Preservation

- Women requiring gonadotoxic treatment can now choose from one or more fertility preservation options. Similar options are available for women who desire to postpone childbearing due to personal reasons.

INDICATIONS FOR FERTILITY PRESERVATION

- ***Malignant Diseases***
- ***Nonmalignant Conditions***
- ***Fertility Decline Associated with Advanced Age***

Malignant Diseases

- Nowadays, lymphoma and leukemia (in young women) as well as breast cancer (in relatively older women but who are still in their reproductive age) can be cured or enter long remission following an aggressive chemotherapy with or without radiotherapy. These cancers in particular and others (such as sarcomas and pelvic cancers) make up the majority of cancer-related indications for fertility preservation interventions, preferably prior to the administration of the gonadotoxic chemo-radio therapy

Nonmalignant Conditions

- Turner syndrome, fragile X permutation, family history of POI.
- high-grade systemic lupus erythematosus or bone marrow ablation followed by allogeneic transplantation for benign bone marrow disorders such as aplastic anemia, sickle cell disease, and thalassemia.
- severe endometriosis have a profound effect on fertility potential owing to diseas natural progression and spread and the surgical interventions for the removal of endometriomas.
- The resection of bilateral benign ovarian tumors such as teratomas .
- Recurrent ovarian torsion .

Fertility Decline Associated with Advanced Age

- Age is the most significant threat to female fertility, as oocyte quality declines with age. Today, more and more women are postponing childbearing due to personal reasons such as graduate education, career choices, lack of a partner, or financial considerations.

CRYOPRESERVATION OF EMBRYOS AND OOCYTES

- Embryo and mature oocyte cryopreservation are the only established effective fertility preservation approaches currently available.
- embryo cryopreservation has now been successfully employed for over than 30 years. Today, the transfer of vitrified (superior to slow freezing) thawed embryos is as effective as the transfer of fresh ones, without a decline in live birth rates.

- the first report of a pregnancy achieved with cryopreserved oocytes by Chen in 1986.
- Mature (MII) oocytes are among the largest cells in the human body and contain the delicate meiotic spindle.
- As oocyte cytoplasm contains a high proportion of water in comparison to other cells, damage due to ice crystal formation was an initial hurdle to oocyte viability after frozen storage.
- Cryopreservation of mature oocytes has also been shown to cause hardening of the zona pellucida, resulting in adverse effects upon fertilization.
- Significant improvement in the fertilization of cryopreserved oocytes was achieved with the use of (ICSI), possibly due to the circumvention of the effects of zona hardening.

vitrification

- The vitrification technique of oocytes as an alternative to slow freezing reduced damage to internal structures and led to improved success rates .
- oocyte vitrification yields remarkable cumulative live birth rates of 60.5% among healthy women who are 35 years old or younger.[28] Women with cancer, however, are expected to have a lower live birth rate likely due to lower oocyte quality caused by the disease.

planning embryo or egg cryopreservation factors should be taken into consideration:

- (1) Age. The younger the woman is at the time of oocyte retrieval and egg/embryo freezing, the higher the live birth rate.
- prepubertal ovaries are not responsive to gonadotropins due to the absence of ovarian receptors to gonadotropins. Prepubertal cancer patients therefore cannot benefit from fertility preservation techniques that require ovarian stimulation.
- Delay in cancer treatment. Oocyte and embryo cryopreservation require controlled ovarian hyperstimulation, delaying the administration of chemotherapy by a minimum of 10-12 days.

- random-start approaches to ovarian hyperstimulation are equally effective, and such delays are not necessary.
- Hormone sensitivity of malignancies. Low estradiol levels during ovarian stimulation are considered safer in the setting of malignancies sensitive to estrogens. The ovarian stimulation protocol should therefore be tailored to the steroid hormone sensitivity of the cancer.
- For example, in the case of estrogen receptor-positive breast cancer, One option is to start stimulation with an aromatase inhibitor on the second or third day of the menstrual cycle followed by addition of daily follicle-stimulating hormone (FSH).

OVARIAN TISSUE CRYOPRESERVATION

- Ovarian tissue cryopreservation is a unique approach to fertility preservation as it is the only option that is suitable for prepubertal girls. In addition, ovarian tissue extraction does not require prior ovarian stimulation, allowing cancer treatments to begin immediately.
- in 2015, Demeestere reported the first live birth following autotransplantation of ovarian tissue extracted before the onset of menarche (during puberty).

Whole Ovary Cryopreservation

- The ovarian cortex harbors the eggs. In most centers worldwide, ovarian cortical tissue is extracted rather than the whole ovary. However, tissue ischemia with loss of follicles remains a common problem after ovarian tissue autotransplantation.
- Whole ovary autotransplantation may overcome this problem.
- The disadvantages include possible reseeding of malignancy, technical difficulties with vascular reanastomosis, and greater risk for cryoinjury during the freezing process of a relatively large tissue volume.

Ovarian Tissue Freezing Techniques and Transplantation Locations

- Cryopreservation of ovarian tissue can be performed using one of two established techniques: slow freezing or rapid freezing (vitrification).
- the vitrification method might become more popular in clinical practice, as happened for vitrification of oocytes.
- The “physiologic” transplantation of frozen-thawed ovarian cortical fragments is orthotopic transplantation, into the remaining ovary, the ovarian fossa, or the broad ligament.
- Orthotopic transplantation provides the ability to achieve a natural pregnancy without the requirement for IVF.

- Heterotopic transplantation (into the subcutaneous space of the forearm, subcutaneous tissue of the abdomen, anterior wall of the abdomen, just beneath the peritoneum, or in the rectus muscle) is advantageous in cases of severe pelvic adhesions, distorted pelvic anatomy, and poor pelvic vasculature due to previous irradiation.

- heterotopic transplantation may produce lower quality oocytes and embryos when compared to the orthotopic approach.These results are likely linked to the less favorable conditions of heterotopic sites in regard to temperature, pressure, reduced paracrine factors, and suboptimal blood supply. To date, a small number of spontaneous live births after.

- live births in women with prior bilateral oophorectomy has only been documented from orthotopic transplantations until the report by Stern et al. in 2013, where frozen-thawed ovarian tissue was transplanted to the anterior abdominal wall.

In Vitro Follicle Maturation

- An alternative to orthotopic or heterotopic transplantation of frozen-thawed ovarian cortical fragments would be to mature follicles in vitro, especially primordial follicles, which constitute the largest pool of follicles stored in the ovary.
- This approach would also allow the patient avoid potential reseeding of cancer cells that might have metastasized to the ovarian tissue.
- patients should be informed that an efficient method of generating mature oocytes in vitro from cryopreserved ovarian cortical tissue does not yet exist.

Combination of Ovarian Tissue Cryopreservation with Other Assisted Reproductive Technologies

- cancer patients with malignancies insensitive to gonadotropins or estrogen may undergo short ovarian stimulation and egg retrieval before the extraction of ovarian tissue for cryopreservation and the initiation of chemotherapy. oocyte aspiration just prior to ovarian tissue cryobanking yielded more oocytes, with a better maturation rate than oocytes retrieved from ex vivo ovarian tissue.

Menopause and Premature Ovarian Failure in the Era of Tissue Cryopreservation

- “radical procedure,” such as unilateral oophorectomy, only marginally affects fertility and the onset of menopause.
- More recent studies found that women with one ovary entered menopause about a year earlier than women with two ovaries.
- summarized the current data on menopause and concluded that “…normal women will experience little if any effect on fertility and age of menopause by having ovarian tissue removed when young.”

What if menopause and its related complications could be physiologically delayed?

- Although the primary goal of ovarian cryopreservation is fertility preservation, transplantation of frozen-thawed ovarian tissue could serve as a physiologic solution to prevent osteoporosis and other menopauserelated disorders.

- excision of ovarian tissue will advance menopause marginally, but it will not reduce natural fertility. If the tissue is autotransplanted at perimenopausal period, sufficient circulating concentrations of sex steroids may be maintained for years and may potentially delay postmenopausal symptoms for even decades.

Potential Complications Resulting from Tissue Transplantation

- Posttransplantation ischemia is likely responsible for follicular loss.
- A live birth following ovarian tissue transplantation utilizing a human decellularized extracellular tissue matrix as a scaffold has been reported.
- This kind of scaffold is thought to aid in the grafted tissue revascularization and, therefore, improve its function and survival;
- Reimplantation of malignant cells together with the grafted ovarian tissue remains a serious concern.

MEDICAL MANAGEMENT OF OVARIAN PROTECTION

- Gonadotropin-releasing hormone (GnRH) agonists have a potential benefit in decreasing ovarian tissue damage while exposed to gonadotoxic chemotherapy agents.

several theories have been proposed:

1-the gonadotoxic chemotherapy induces an accelerated rate of follicular demise due to low estrogen and inhibin levels resulting in supraphysiologic FSH secretion. high FSH levels accelerate the rate of preantral follicle recruitment to enter the unidirectional process of maturation, resulting in their further exposure to gonadotoxic effects of chemotherapy, and in an accelerated follicular demise. The administration of GnRH agonists could interrupt this vicious cycle by inducing pituitary desensitization, preventing the increase in FSH .

- (2) Decrease in utero-ovarian perfusion. Continuous exposure to a GnRH agonist leads to decreased levels of FSH and LH that result in hypoestrogenic state. Hypoestrogenic state decreases utero-ovarian perfusion. which in turn brings to lower total cumulative exposure of the ovaries to the circulating chemotherapeutic agents.

FUTURE PROSPECTS

- The general field of tissue cryopreservation is evolving and is likely to provide additional achievements in the near future;

Thank you for your attention